Remarks

Claim 1 is hereby amended. Claims 27-33 are newly submitted. Claims 2, 3, 5 and 7 were previously cancelled. Claims 9 to 26 have been previously withdrawn. Claims 1, 4, 6, 8 and 27-33 are therefore pending in the application. No new matter has been added by way of the present amendments.

Claim 1 as amended currently reads:

> *" A method for stimulating or activating differentiation, proliferation and egress of at least one immune cell type in a human patient having neutropenia, the method comprising: administering to said patient a therapeutically effective dose of at least one S100 protein selected from the group consisting of: S100A8, S100A9 and S100A12 homodimers, and S100A8/S100A9 heterodimers; and measuring the level of circulating mature immune cells in circulating blood of said patient."*

New claim 27 reads:

> *"A method for treating neutropenia in a human patient suffering therefrom, the method comprising: ascertaining that the patient has neutropenia; and administering to said patient a therapeutically effective dose of at least one S100 protein selected from the group consisting of: S100A8, S100A9 and S100A12 homodimers, and S100A8/S100A9 heterodimers."*

New claim 31 reads:

> *"A method for treating neutropenia in a human patient suffering therefrom, the method comprising: administering to said patient a therapeutically effective dose of at least one S100 protein selected from the group consisting of: S100A8, S100A9 and S100A12 homodimers, and S100A8/S100A9 heterodimers; and monitoring egress of mature immune cells from bone marrow to peripheral circulation of said patient."*

No new matter has been added by the present amendments.

Claim rejections

The examiner rejects claims 1, 2, 4 and 8 as presumably obvious over Halle *et al.* (US 2003/0003482) because this reference teaches the use of MRP8 and/or MRP14 for treating and/or preventing skin diseases and wounds in patients. Claim 1 as amended recites "*measuring the level of circulating mature immune cells in circulating blood of said patient*", which is a step that is clearly distinguishable from the treatment of skin wounds and diabetic ulcers and therefore patentably distinct. Withdrawal of this rejection is therefore respectfully requested.

Several factual inquiries must be made to determine obviousness or non-obviousness of patent application claims under 35 U.S.C. § 103. The basic inquiry was set forth in Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966) and includes: (1) determining of the scope and content of the prior art; (2) comparing the differences between the prior art and the claims at issue; and (3) ascertaining the level of ordinary skill in the pertinent art. See also KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1734 (2007). In KSR, the Court admonished that it is important to identify reasons to combine the prior art elements in the manner claimed. The KSR Court stated that when considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions". Id. at 1396. An Examiner bears the initial burden of presenting a *prima facie* case of obviousness. In re Oetiker, 977 F.2d 1443, 1445-1446 (Fed. Cir. 1992). Once the Examiner presents a *prima facie* case, the Applicants may present evidence of secondary considerations. Obviousness is then determined on the basis of the evidence as a whole. Id.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness based upon governing case law including KSR, the examination guidelines for determining obviousness under 35 U.S.C. § 103 (M.P.E.P. Section 2141), and decisions of the Board of Patent Appeals and Interferences applying same. The Examiner provides no reason to combine Hall et al. with Fescari *et al.* and Aboulafia. In addition, the combination of Hall et al. with Fescari *et al.* and Aboulafia does not lead one skilled in the art to all elements claimed.

Halle *et al.* teaches treatment of wound healing by increasing the quantity of MRP polypeptide, thereby inducing proliferation of one type of MRP-responsive cell: the keratinocyte. The present

invention is however directed at the treatment of neutropenia by increasing differentiation, proliferation and egress of others types of MPR-responsive cells, i.e. neutrophils, monocytes, macrophages, platelets, synoviocytes, leukocytes or phagocytic cells NOT keratinocytes.

As stated in MPEP section 706.02(j), "*To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.*" Ex parte Clapp, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). ... "*It is important for an examiner to properly communicate the basis for a rejection so that the issues can be identified early and the applicant can be given fair opportunity to reply. ... it is important that the written record clearly explain the rationale for decisions made during prosecution of the application.*" The Examiner fails, however, to provide any articulated reasoning with rational underpinning to support the legal conclusion of obviousness as required by KSR. See KSR, 127 S. Ct. at 1740-41.

A *prima facie* case has not been made because the Examiner's conclusion lacks rational underpinning

When comparing the differences between the prior art and the claimed invention, one must cast his mind back to the time of the invention and resist the temptation to employ hindsight, which may cause one to misinterpret the simplicity of a solution as obvious. See In re Kotzab, 217 F.3d 1365, 1369 (Fed. Cir. 2000). Therefore, it is important to note that obviousness cannot be established by simply combining the teachings of the prior art to produce the claimed invention. KSR, 127 S. Ct. at 1741; In re Napier, 55 F.3d 610, 613 (Fed. Cir. 1995). In KSR, the Court reaffirmed that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." KSR, 127 S. Ct. at 1741. Indeed, often it will "be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine" previously known elements. Id.

A recent case from the Board of Patent Appeals and Interferences (the "Board") exemplifies that the Board rejects, as it must, merely conclusory statements lacking rational underpinning. In Ex parte Girouard et al.., Appeal 2007-3307 (BPAI 2008), the Board stated that KSR requires an

explicit analysis, when a conclusion of obviousness is based on interrelated teachings of multiple patents, of the effects of demands known to the design community or present in the marketplace and the background knowledge possessed by a person having ordinary skill in the art. Id. The Board also stated that the obviousness analysis is not complete until an explanation is provided as to why one having ordinary skill in the art would have been led to apply a teaching, particularly in light of the contrary teachings pointed out by the applicant(s). The Board found that the Examiner had failed to provide any articulated reasoning with rational underpinning to support a legal conclusion of obviousness.

As the combination of the two references teaching engine supports associated with snowmobile frames is improper (see Ex parte Girouard *et al.*), the combination of two references having diverging objective, one teaching a method for the treatment of diabetic ulcers and the other teaching that HIV patients frequently have decubitus ulcers, is also improper. It is not sufficient to conclude that all ulcers may be found in HIV AIDS patients and because all AIDS patients are neutropenic ... therefore neutropenia can be treated with MRP8 and/or MRP14. The obviousness analysis is not complete as the Examiner has failed to provide an explanation as to how one having ordinary skill in the art would have been led to apply the teachings of Halle *et al.* of treatment of diabetic ulcers with MRP8 and/or 14 to the teachings of Nicastri and Aboulafia that several AIDS patients have pressure ulcers, therefore treatment of neutropenia in AIDS patients with MRP8 and/or -14 is obvious.

Hall *et al.* is clearly directed toward treatment of wounds NOT neutropenia. The Examiner bridges the gap by citing that Nicastri and Aboulafia teach that HIV patients frequently have decubitus ulcers and that therefore one could use MRP-8/14 for treating chronic wounds such as decubitus ulcers in patients with HIV AIDS *i.e. neutropenic patients*. Indeed, that gap can not be bridged without the benefit of hindsight. In addition, Hall *et al.* teaches away from Aboulafia since Hall *et al.* is clear in that the ONLY ulcer that responds to his treatment is the diabetic ulcer and no other type of ulcer; see page 12, column 2:

> of the healthy patients. Strong labeling was observed at the edge (corresponds to the hyperproliferative epithelium in normally healing wounds) of the venous ulcer wound. This demonstrates that there is no aberrant regulation in the venous ulcer. "Aberrant regulation" of the MRP8/MRP14 heterodimers, and/or their individual components in combination, in association with skin diseases, wounds and/or wound-healing disturbances is defined as a strength of expression which turns out to be markedly reduced, as compared with that seen in normal wound healing, in the cells, in the body fluids, in the wound liquid and/or in the skin. By contrast, a different result was surprisingly observed in the case of the labeling of the diabetic ulcer: only very weak labeling as observed at the edge of the wound. This shows that MRP14 is only expressed to a decreased extent at the edge of the diabetic ulcer wound but not at the edge of the venous ulcer wound or in normally healing wounds. The fact that the lack of MRP14 is observed in the cell layer which is required for proliferation and thus reepithelialization indicates that the wound-healing disturbance in diabetic patients could be caused by an inhibition of proliferation due to the content of MRP8/MRP14 polypeptide being too low.

To generalize the teaching of Halle *et al.* to other types of ulcers, and then to all forms of chronic wounds, ... **and then to neutropenia in general** since they often accompany chronic wounds amounts to hindsight that is clearly unacceptable. As such, the Examiner has failed to establish a *prima facie* case of obviousness and is requested to withdraw the rejection. Should the Examiner persist in his interpretation of the cited prior art, he is respectfully requested to clearly and specifically pinpoint the relevant portions of the documents providing: a) some suggestion or motivation to combine; b) reasonable expectation of success; and c) teaching or suggestion of all claim limitations.

Therefore, it is submitted that all claims as amended are not obvious over the references by Halle *et al.* in view of Nicastri and Aboulafia. The rejection must be withdrawn.

It is submitted, therefore, that the claims are in condition for allowance. Reconsideration of the examiner's rejections is respectfully requested and allowance of claims 1, 4, 6, 8 and 27-33 at an early date is earnestly solicited.

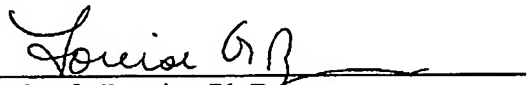
In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Please find enclosed herewith form PTO/SB/30 requesting continued examination of the above-referenced application. The Commissioner is hereby authorized to charge the RCE fee in the amount of $405.00 to our Account No. 19-5113.

No other fees are believed to be required by the present response. However, should this be an error, authorization is hereby given to charge deposit account 19-5113 for any underpayment or to credit any overpayment.

Respectfully submitted,

UNIVERSITÉ LAVAL



Louise G. Bernier, Ph.D.
Reg. No. 38,791
Agent for the Applicant
OGILVY RENAULT, LLP
Customer number: 020988